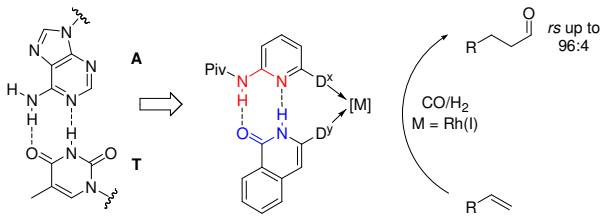
Self-Assembly of Bidentate Ligands for Combinatorial Homogeneous Catalysis: Methanol-Stable Platforms Analogous to the Adenine-Thymine Base Pair

Jörg Wieland, Christoph Waloch, Bernhard Breit*

Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg, Albertstr. 21, 79104 Freiburg i. Br., Germany.
bernhard.breit@organik.chemie.uni-freiburg.de

Concept

Combinatorial methods have recently been introduced to homogeneous metal complex catalysis as a means to accelerate the catalyst discovery process.[1] Many elegant solutions for high throughput screening have been developed.[2] However, the combinatorial approach suffers from the limited access to structurally diverse and useful ligand libraries, in particular in the important field of bidentate ligands, whose often complex synthesis render them unsuited for automated approaches. We recently introduced an alternative to the classical covalent bidentate ligand synthesis, which relies on self-assembly of monodentate ligands through complementary hydrogen-bonding to give defined heterodimeric bidentate ligands on the basis of an A-T base pair analogue, the aminopyridine-isoquinolone system (Scheme 1).[3,4]

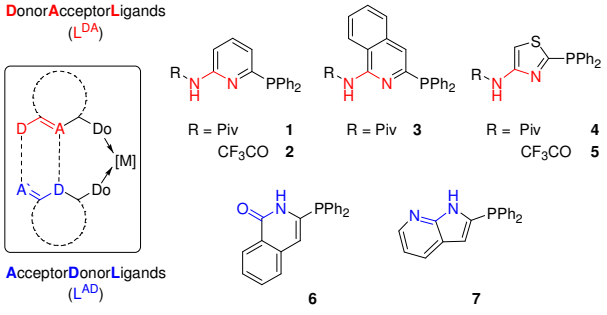


Scheme 1: An A-T base-pair model as a platform for the self-assembly of chiral monodentate to chiral bidentate ligands through complementary hydrogen-bonding for combinatorial asymmetric catalysis.

After successful variation of the donor functions D^x/D^y,[4] we were strongly interested, if this approach is restricted to the aminopyridine/ isoquinoline self-assembly system, or whether a structural variation of the heterocyclic platform is possible.

Results

We herein report on the development of the first self-assembly ligand library based on new heterocyclic A-T base pair analogue platforms (Scheme 2), comprising of heterocycle functionalized phosphines **1**-**5** as A-analogue **D**onor**A**cceptor**L**igands (L^{DA} in Scheme 2) and the known isquinolone **6** and the new 7-azaindole system **7** as T-analogue **A**cceptor**D**onor**L**igands (L^{AD} in Scheme 2).[5]



Scheme 2: A library of ligands with complementary hydrogen-bonding motifs. D = hydrogen-bond donor. A = hydrogen-bond acceptor. Piv = pivaloyl.

All heterodimer combinations were investigated by ^{31}P-NMR-spectroscopy as their Pt-complexes and showed typical coupling constants for *cis*-Pt-dimers. X-ray crystals of *cis*-[Cl_2Pt(**3**/**7**)] (Figure 1a) and *cis*-[Cl_2Pt(**4**/**6**)] (Figure 1b) confirm the complementary hydrogen-bonding reminiscent of the Watson-Crick base pairing.

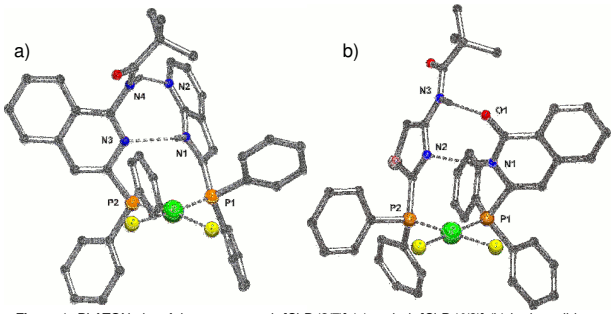
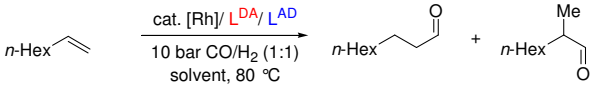


Figure 1: PLATON plot of the structures *cis*-[Cl_2Pt(**3**/**7**)] (a) and *cis*-[Cl_2Pt(**4**/**6**)] (b) in the solid state. Selected interatomic distances [Å] and angles [°]: a) *cis*-[Cl_2Pt(**3**/**7**)] Pt-P1 2.2417(6), Pt-P2 2.2517(6), N1···N3 2.910(3), N4···N2 2.987(3), P1-Pt-P2 99.01(2), N1-H···N3 129.0, N4-H···N2 153.7. b) *cis*-[Cl_2Pt(**4**/**6**)]: Pt-P1 2.2609(5), Pt-P2 2.2331(6), N1···N2 2.992(3), N3···O1 3.038(3); P1-Pt-P2 97.42(2), N1-H···N2 159.0, N3-H···O1 166.0. Pt green, C dark gray, H light gray, N blue, P orange, O red, S pink, Cl yellow; H atoms bound to C atoms are omitted for clarity.

In additonal hydroformylation experiments, using 1-octene as substrate, high *l*inear:*b*ranched ratios (up to >99:1, table 1, colorless background) could be achieved. The observed regioselectivities confirm that in all cases bidentate ligand catalysts are the kinetically competent species. While our „first generation" self-assembly ligand system was very susceptible to protic solvents,[4] the new thiazole based ligand combinations **4**/**6** and **5**/**6** exhibit a much more stable hydrogen bonding framework. This allowed us for the first time to perform a hydroformylation in a protic solvent such as methanol (Table 1, grey background). Even under these conditions, stable heterodimeric catalysts based on hydrogen bonds are formed, giving very high *l*:*b* ratios (up to 97:3).

Table 1: *l*inear:*b*ranched (*l*:*b*) regioselectivities[a] of the rhodium-catalyzed hydroformylation of 1-octene in toluene and methanol for self-assembled bidentate ligands derived from donor-acceptor (L^{DA}; **1**-**5**) and acceptor-donor ligands (L^{AD}; **6**, **7**).[b]



		*l*inear				*b*ranched
$L^{DA}\rightarrow$ / $L^{AD}\downarrow$	solvent	**1**	**2**	**3**	**4**	**5**
6	toluene	94:6	96:4	95:5	98:2	**> 99:1**
	MeOH	82:18	79:21	79:21	**97:3**	**96:4**
7	toluene	89:11	96:4	95:5	95:5	**>99:1**
	MeOH	77:23	80:20	78:22	89:11	85:15

[a] Regioselectivity: *l*inear to *b*ranched determined by GC analysis; complete conversion was reached in all cases.
[b] Reaction conditions: $[Rh(CO)_2(acac)]$, [Rh]:L^{DA}:L^{AD}:1-octene = 1:10:10:7500, 10 bar CO/H_2 (1:1), solvent, c_0 (1-octene) = 2.91 M, 12 h.
Catalyst preformation: 5 bar CO/H_2 (1:1), 30 min, RT→80 °C.

Conclusion

In conclusion, the combinatorial self-assembly of monodentate to bidentate ligands for homogeneous catalysis is a very promising approach to the development of new and better catalysts. Herein, we have demonstrated that variation of the heterocyclic self-assembly platform has an enormous impact on the properties of the resulting catalyst. New hydroformylation catalysts with excellent activities and outstanding regioselectivities, even in protic solvents such as methanol, were identified. This result is an important extension of the application scope of self-assembled catalysts based on hydrogen-bonding. New applications in homogeneous catalysis are expected to emerge soon.

Acknowledgments
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Literature
[1] C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, *103*, 3071-3100. [2] M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem.* **2003**, *115*, 814-817; J. M. Takacs, D. S. Reddy, S. A. Moteki, D. Wu, H. Palencia, *J. Am. Chem. Soc.* **2004**, *126*, 4494-4495; V. F. Slagt, M. Röder, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *J. Am. Chem. Soc.* **2004**, *126*, 4056-4057. [3] B. Breit, W. Seiche, *J. Am. Chem. Soc.* **2003**, *125*, 6608-6609. [4] a) B. Breit, W. Seiche, *Angew. Chem.* **2005**, *117*, 1666-1669; b) Breit, F. Chevallier, *Angew. Chem.* **2006**, *118*, 1629-1632; c) M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, *128*, 4188-4189. [5] J. Wieland, C. Waloch, M. Keller, B. Breit, *Angew. Chem.* **2007**, *119*, 3097-3099.